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Filed : November 20, 2001

### REMARKS

Claims 1-18 were pending. New Claims 19-25 have been added and Claims 1-18 have been canceled. Upon the entry of the Amendments, Claims 19-25 are pending in this application. No new matter has been added by the amendments. Support for the new claims is found throughout the specification and the original claims as filed. For example, support for the new claims can be found in canceled Claim 1; the discussion of Example 1 from page 11, line 17 to page 14, lines 19; Figure 1 and the discussion thereof at page 14, line 21 to page 15 and line 9; the discussion at page 7, line 32 to page 8, line 2; the discussion at page 6, line 26-27, the discussion at page 6, lines 17-22; the discussion at page 7, line 5-9; the discussion at page 6, line 26-27, and the specification at page 12, line 30. As such, the Amendments are fully supported by the application as originally filed. Thus, no new matter has been added by the amendments above. Applicants respectfully request the entry of the amendments.

Applicants respectfully request entry of the amendments and reconsideration of the application in view of the amendments and the remarks set forth below. A three month extension of time is also requested.

#### Affirmation of Oral Election in Response to Restriction Requirement

Applicants affirm the oral election of Group I (Claims 1-17) made by Che Swyden Chereskin, Ph.D., Registration No. 41,466, during the telephone conversation with the Examiner on November 17, 2002. Applicants note, however, that the oral election of Group I was made with traverse. Applicants traverse the restriction requirement because the examination of Groups I and II would not add an unreasonable search burden to the Examiner in view of the fact that Claim 18 of Group II is directed to a kit for substantially exclusively using the method of the claims of Group I.

Regardless, Claims 1-18 have been cancelled as above. Claims 1-17 have been canceled in view of the addition of new Claims 19-25. Claim 18 has been canceled as being non-elected. New Claims 19-25 are directed to a method of identifying a mutation in a nucleotide sequence. Applicants respectfully submit that Claims 19-25 belong to Group I as identified by the Examiner at page 2 of the Office Action. Claims 1-17 were directed to subject matter of the same statutory class as that now recited in claims 19-25.

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### Specification

The specification has been amended to capitalize the trademarks "Tween-20<sup>TM</sup>" and "Triton X-100<sup>TM</sup>" as suggested by the Examiner.

### Rejection Under 35 U.S.C. § 112

Claims 1-17 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully disagree. Nevertheless, to facilitate prosecution, Claims 1-17 have been canceled in favor of new Claims 19-25. Applicants submit that the new claims clearly define the invention and are believed to be definite.

In the Office Action, Claims 1-17 were rejected as allegedly being indefinite. The Examiner alleged that the claims should be amended either to add additional method steps or clarify how detection of hybridization accomplishes the recited objective. New Claim 19 recites a multi-step method for detecting the hybridization of a sample to an immobilized probe. The samples are biotinylated so that detection of sample binding to a probe can be detected by determining the optical density generated when an avidin-labeled degradation enzyme and appropriate substrate are provided to the sample/immobilized probe hybrid. Accordingly, Claim 19 is definite.

Claims 1-17 were rejected for reciting various phrases. These phrases included "corresponding to the DNA sequence to be identified", "the amine group of the microwell," "ice cold", "the probe of microwell", and "residual DNA fragments". These terms do not appear in the new claims.

We also note that particular claims were rejected for either reciting a trademark in an improper format or for using the "/" symbol. The new claims have been drafted to avoid using these terms.

### Discussion of Rejection Under 35 U.S.C. § 103

The Examiner rejected Claims 1-17 under 35 U.S.C. § 103 (a) as being unpatentable over Saiki *et al.*, Proc Natl Acad Sci USA 86:6230-6234, 1989 ("Saiki") in combination with one or more of Zammattéo *et al.* (Analytical Biochemistry 236:85-96, 1996, hereinafter "Zammattéo"),

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Rasmussen *et al.* (Analytical Biochemistry 198:134-142, 1991), Zammattéo *et al.* (Journal of Virological Method 55:185-197, 1995, hereinafter "Zammattéo 95"), Felder *et al.* (U.S. Patent No. 6,232,066 B1), Villeponteau *et al.* (U.S. Patent No. 5,776,679), Bogdanov (U.S. Patent No. 6,245,507 B1), Zreiqat *et al.* (Molecular Biotechnology, 10:107-113, 1998), Kit *et al.* (U.S. Patent No. 4,711,850), Stebbins *et al.* (Analytical Biochemistry 248:246-250, 1997) and Rueger (U.S. Patent No. 5,610,021). Applicants respectfully disagree. However, solely in order to expedite prosecution, Claims 1-17 have been canceled as discussed above, and, thus, the rejection is moot. Furthermore, if such references were applied in the same manner, Applicants respectfully submit that Claims 19-25 are allowable in light of the arguments set forth below.

#### Patentability of Claims 19-25

The pending claims are patentable over the art cited by the Examiner. The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984). To articulate a *prima facie* case of obviousness, the Examiner must cite one or more references that taken alone or together can be modified or combined to achieve the claimed invention. *See, e.g., In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). There is no suggestion or motivation to modify or combine a reference or references if the proposed modification would render the prior art being modified unsatisfactory for its intended purpose. *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants submit that the references discussed above taken alone or in combination do not articulate a *prima facie* case of obviousness. Specifically, one of ordinary skill in the art would not have been motivated to modify the teachings of Saiki *et al.*, PNAS USA 86:6230-6234 1989 ("Saiki") in view of Zammattéo *et al.*, Anal. Biochem. 236:85-94 1996 ("Zammattéo") or any of the other cited references to achieve the claimed invention. The combination of Saiki and Zammattéo proposed by the Examiner would modify Saiki, rendering it unsatisfactory for its intended purpose because Saiki teaches attaching probes through the 3-prime position of the probe using homopolymer tails.

Saiki taught the preparation of nucleotide probes with long homopolymer tails using a terminal deoxyribonucleotidyltransferase. Saiki at 8280, second column. The terminal

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deoxyribonucleotidyltransferase enzyme catalyzes template-independent extension of the 3-prime end of a DNA strand one nucleotide at a time. The Saiki probes were then covalently bound by UV irradiation to a nylon membrane.

The Saiki reference discusses the importance of using a 3-prime fixation method where the probes have "long" 3-prime tails. For example, in the abstract, Saiki states that "[d]ue to their long length, the tails are bound to the nylon, leaving the oligonucleotide probe free to hybridize." Further, Saiki taught that hybridization improved, possibly due to a spacer effect "by increasing the distance between the nylon membrane and the terminal oligonucleotide probe." *Id.* at 6231, second column.

In contrast to Saiki, the teachings of Zammatteo provide for a 5-prime fixation method. Zammatteo taught the amination of polystyrene microwells and attaching DNA probes to the microwells via the probe's 5-prime phosphate group. No spacer is attached to the probes prior to covalent bonding to the probes to the microwells. Little or no "spacer effect" would be expected when one attaches a probe to a matrix using the teachings of Zammatteo. The other references relied on in the Office Action are directed to other features of the claimed invention different from Zammatteo and Saiki. Accordingly, these references do not cure the deficiency of the proposed Saiki-Zammatteo combination.

In light of this discussion, Applicants submit that the teachings of Zammatteo are not freely substitutable for those of Saiki because the two references use different attachment methods to achieve the desired results. Accordingly, Applicants submit that one of ordinary skill in the art would not have been motivated to modify the teachings of Saiki and Zammatteo to achieve the claimed invention. Additionally, the other references cited by the Examiner do not remedy the substantive deficiencies of Saiki and Zammatteo references discussed above. Therefore, the claimed invention is also nonobvious in view of these other references, either taken alone or in combination.

### **CONCLUSION**

In view of Applicants' amendments to the claims and the foregoing remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns, which might prevent the prompt allowance of the

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application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Respectfully submitted,

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Dated: May 20, 2003

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